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ScienceDirect

Radiology of Infectious Diseases 1 (2015) 83–87

www.elsevier.com/locate/jrid

Research article

Altered brain functions in HIV positive patients free of HIV- associated neurocognitive disorders: A MRI study during unilateral hand movements

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Received 4 October 2014; accepted 10 January 2015
Available online 2 March 2015

Abstract

This paper aimed to investigate the brain activity of human immunodeficiency virus (HIV) positive patients with normal cognition during unilateral hand movement and whether highly active antiretroviral therapy (HAART) could affect the brain function. Functional magnetic resonance imaging (fMRI) was performed for 60 HIV positive (HIV+) subjects and −42 healthy age-matched right-handed control subjects. Each subject was evaluated by the neuropsychological test and examined with fMRI during left and right hand movement tasks. HIV+ subjects showed greater activation in anterior cingulum, precuneus, occipital lobes, ipsilateral postcentral gyrus and contralateral cerebellum compared with control group during right hand movement task. However, during left hand movement no statistically significant difference was detected between these two groups. HAART medication for HIV+ subjects lowered the increased activity to normal level. Meanwhile patients receiving the regimen of zidovudine, lamivudine and efavirenz showed lower activity at bilateral caudate and ipsilateral inferior frontal gyrus in comparison with subjects receiving other HAART regimens. Therefore, HIV+ subjects demonstrated brain asymmetry in motor cortex, with increased activity present during right hand movement but absent during left hand movement. HAART proves effective in HIV+ subjects even with normal cognition and the specific regimen of HAART could prevent cerebral abnormal functions. Meanwhile, this study validates that during motor tasks, fMRI can detect the brain signal changes prior to the occurrences of other HIV- associated dysfunctions.

Keywords: HIV; fMRI; Motor cortex; Asymmetry; HAART

1. Introduction

By the end of 2011, there are over 34 million people worldwide living with human immunodeficiency virus (HIV) (WHO), which could exert devastating effects on immune system and result in acquired immunodeficiency syndrome (AIDS). Along with the advent of highly active antiretroviral therapy (HAART), the incidence of HIV- associated neurocognitive disorders (HAND) has been dramatically brought down. However, approximately 50% of individuals infected with human immunodeficiency virus-1 (HIV) are reported still with HAND [1,2]. Subjects with HAND may present deficits in multiple cognitive domains, including attention, executive function, learning, memory, and motor speed [3,4].

Early diagnosis of HIV before HAND is difficult since the injury is clinically silent and asymptomatic. Recently, blood oxygen level dependent (BOLD) neuroimaging has been utilized to assess the neurophysiologic effects of HIV in early stage. Previous research by resting-state functional magnetic resonance imaging (rs-fMRI) found that HIV+ patients had lower intranetwork correlations in the default mode, control, and salience networks, but had no changes in the sensorimotor (SMN) or dorsal attention (DAN) networks [5]. Meanwhile the

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Peer review under responsibility of Beijing You'an Hospital affiliated to Capital Medical University.

http://dx.doi.org/10.1016/j.jrid.2015.02.009

lateral occipital cortex (LOC) network was found different by comparison of the maps between HIV patients and the control group during the rest-state functional connectivity [6]. Additionally, task-related fMRI revealed that HIV patients with normal cognition or mild dementia showed hypoactivation of the normal attention network but increased usage of reserve brain regions during attention-requiring tasks, such as working memory and tracking moving targets [7–9]. Besides, the activation by visual attention was greater than that by working memory task and f the deactivation differed with grades of difficulties [10].

Since previous researches mainly focused on HIV+ patients with HAND, this stud employed unilateral hand movement tasks to test whether cerebral signal changes of HIV+ subjects could be detected prior to occurrence of HAND. Furthermore the correlation between different manifestations of HIV+ subjects without cognitive deficits and medication treatments was examined and the effects of specific regimen of HAART were explored.

2. Materials and methods

2.1. Participants

Sixty right-handed HIV+ patients (HIV+) and forty-two right-handed healthy control subjects (HIV−) were recruited for this study. All subjects underwent clinical assessment and neuropsychological test before MR scan. All participants had signed the informed consent approved by Ethnic Committee of Beijing YouAn Hospital, Capital Medical University. HIV+ subjects should fulfill the following standards: (1) HIV-positive; (2) without other chronic or neuropsychological diseases; (3) taking HAART for at least 2 months or without treatment; (4) free of HAND and other opportunistic infections. 29 out of the 60 HIV+ patients (48%) were taking HAART and had been on a stable regimen for at least 2 months before the test. The control subjects should meet following standards: (1) HIV-seronegative; (2) having no history of other neurological illnesses or drug abuse. Medical records were reviewed for neurologic signs and symptoms as well as $CD4^+$ cell count (cells/mm^3).

2.2. Neuropsychological evaluation

All HIV+ individuals were evaluated by HIV Dementia Scale (HDS), a rapid and reliable screening tool [11]. HDS, widely used for screening dementia comprised four tasks: memory, attention, psychomotor, and construction. A sum score would be calculated based on each domain. HDS scores of all HIV+ subjects in this study were >10, which proved absence of HAND.

2.3. MRI data acquisition

Imaging was performed on a Siemens TIM Trio 3T MR scanner (Siemens, Erlangen, Germany) with a 32-channel head coil at Beijing YouAn Hospital, Capital Medical University. The structural whole-brain scans utilized the high resolution 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR = 1900 ms, TE = 2.52 ms, inversion time = 900 ms, flip angle = 8°, field of view = 250 × 250 mm, matrix = 256 × 256, slice thickness = 1 mm) to construct T2 weighted image and diffusion weighted image (DWI). All scans were conducted to visualize the existence of other central nervous system abnormities such as ischemia, hemorrhage and stroke.

Task-related fMRI was performed using a gradient EPI sequence (TR = 3000 ms, TE = 30 ms, view = 250 × 250 mm, matrix = 96 × 96, axial 35 slices, flip angle = 90°, slice thickness = 3.5 mm with no gap). The block-based motor paradigm consisted of 100 scans with 3 dummy scans per task. There were in total five blocks, each comprising alternated 10 scans during tasks and 10 scans duringrest conditions'. Every subject received a training session before fMRI scan and underwent two motor-related experiments, which included left-hand and right-hand squeeze at a certain frequency (1 time/s), defined as unilateral hand movements. Instructions during the scan were shown on the screen which could be seen through a mirror in front of the patient (ESys fMRI, Invivo, USA).

2.4. Data analysis

fMRI data were processed using the SPM8 software (Wellcome Department of Cognitive Neurology, London, UK), implemented in Matlab v8.0 (Mathworks, Inc., Sherborn, MA). The preprocessing included slice timing correction, motion correction, normalization, and spatial smoothing with an 8 × 8 × 8 mm full-width at half maximum (FWHW) Gaussian kernel. The task-related effects on BOLD signals were evaluated by a general linear model (GLM). The random-effect repressor convolved with a canonical hemodynamic response function was based on definition of the hand movement and rest condition. Brain activation maps were results from the statistical parametric t-images to investigate the positive or negative effects in each group. Within the group, one-sample t-test was conducted to examine the correlation between subjects of the HIV+ group and those of the control group, which showed the voxels exceeded $p < 0.05$ family-wise error corrected (FWE) level and $k > 10$. Between groups, two-sample t-test was used as second level analysis. Statistical results were showed with a threshold of $p < 0.001$uncorrected for multiple comparison and $k > 10$.

3. Results

Subjects with other central nervous system abnormities or big head motion during the scans were excluded. There are respectively fifty-one (47 males and 4 females) HIV+ subjects and thirty-nine (19 males and 20 females) healthy control subjects eligible for left-hand movement analysis and fifty-seven (49males and 8 females) HIV+ subjects and thirty-nine (19 males and 20 females) healthy controls = subjects for right-hand movement analysis. No statistically significant

Table 1
Demographics and laboratory values for HIV+ and HIV− control subjects of two groups.

	Left-hand movements		Right-hand movements	
	HIV+	HIV− (control)	HIV+	HIV− (control)
Age, ±SD (year)	39 ± 10	32 ± 9	39 ± 10	32 ± 9
Sex	47M, 4F	19M, 20F	49M, 8F	19M, 20F
Taking HAART, %	39%	NA	42%	NA
CD4 cell count	197	NA	194	NA

Abbreviations: M-male; F-female; HAART-highly active antiretroviral therapy; NA-not applicable.

difference of age between the HIV+ and control group (39 ± 10 vs. 32 ± 9 years) was detected. CD4 cell count, for assessment of disease progression, was similar in the HIV+ group for left-hand movement analysis and HIV+ group for right-hand movement analysis (Table 1). HIV+ group was subdivided into those with HAART (21males and 7 females, aged averagely 38 years old, CD4 cell count 225) and those without HAART (28 males and 1 female, aged averagely 40 years old, CD4 cell count 165).

3.1. HIV asymmetrically affects BOLD signals during unilateral hand movement

Both left and right hand movement tasks activated contralateral precentral and postcentral cortex, ipsilateral cerebellum and supplementary motor cortex in HIV+ and control groups (Figs. 1A, 1B, 2A, and 2B). In addition, left-hand movement also activated bilateral temporal lobes and contralateral cerebellum in the two groups. Two-sample t-test found that there was no significant difference between HIV+ and control groups during left-hand movement (Fig. 1C).

During the right hand movement task, bilateral temporal lobes and contralateral cerebellum were also activated in HIV+ group, but such activation decreased or disappeared in the control group (Fig. 2A and B). Two-sample t-test demonstrated an increase of BOLD signals in anterior cingulum, precuneus, occipital lobes, ipsilateral postcentral gyrus, and contralateral cerebellum in HIV+ group (Fig. 2C).

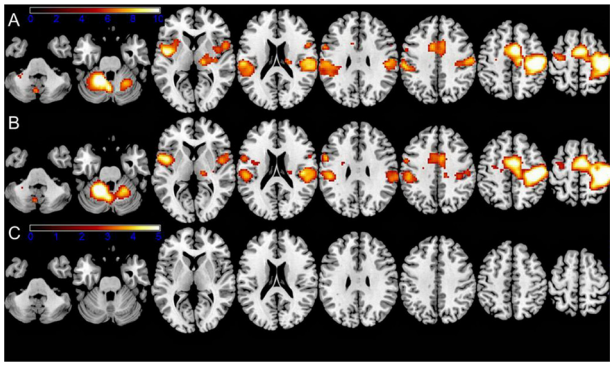

Fig. 1. Brain activation associated with left-hand movement in healthy group (A) and HIV patients (B). No difference was found in the BOLD signals between healthy group and HIV patients (C).

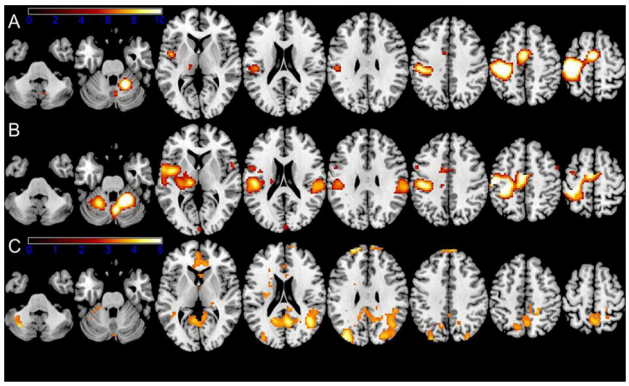

Fig. 2. Brain activation associated with right-hand movement in healthy group (A) and HIV patients (B). Compared with the healthy group, HIV patients presented with increased BOLD signals in anterior cingulum, precuneus, occipital lobes, ipsilateral postcentral gyrus and contralateral cerebellum in (C).

3.2. HAART affects BOLD signals in the HIV+ subjects

Since the HIV+ group composed of patients with and without HAART, patients without HAART (non-HAART) were compared with control subjects to exclude the influence of medical treatment on BOLD signals. Compared with control group, non-HAART group also presented with increased BOLD signals in the cerebral area reported in previous analysis during right-hand movement. Besides, posterior cingulum and fusiform were also documented with increased BOLD signals in non-HAART group (Fig. 3).

Additionally, patients with and without HAART were compared to ascertain the effects of HAART. The findings revealed that HAART could slightly enhance BOLD signals in the right postcentral gyrus, but greatly attenuated BOLD signals in the fusiform (Fig. 4A and B).

3.3. Different drug combinations have varying effects on brain activation

HAART is a treatment with combined drugs. Since clinical trials had unveiled better therapeutic effects of combined Zidovudine (AZT), lamivudine (3TC) and efavirenz (EFV) displayed than other regimens [12,13], the HAART group in this study was subdivided into Zidovudine (AZT), lamivudine (3TC) and efavirenz (EFV) treatment (ATE) group (12 males, aged averagely 35 years old, CD4 cell count 206)and other

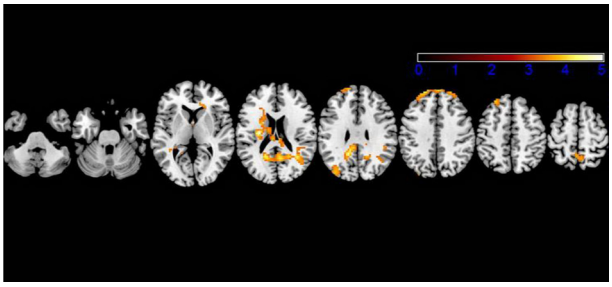

Fig. 3. Brain activation associated with right-hand movement in healthy group and HIV patients without receiving HAART.

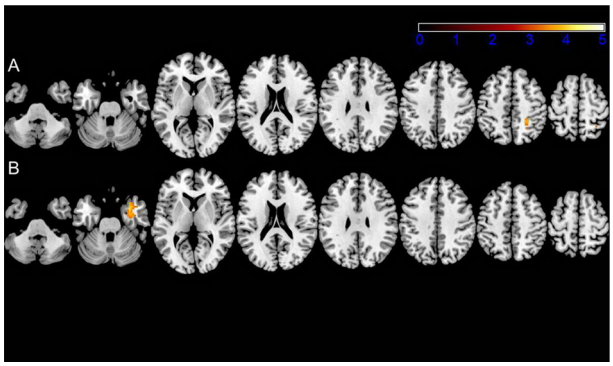

Fig. 4. Brain activation associated with right-hand movement in HIV patients with and without receiving HAART. HAART increased BOLD signals in the right postcentral gyrus (A), but decreased signals in fusiform (B).

regimen group (9 males and 7 females, aged averagely 39 years old, CD4 cell count 238). This study found that the ATE group manifested lower brain activation than other subjects in bilateral caudate and ipsilateral inferior frontal gyrus.

4. Discussion

HIV could result in neuropsychological alterations. Even with the extensive applications of HAART, some cognitive impairments have still been reported [14,15]. This study analyzed the fMRI findings of HIV+ patients with normal cognition and HIV− patients (control) in order to investigate their differences during unilateral hand movement tasks. The findings demonstrated that brain activation of HIV+ and control group was different during right hand movement task, but similar during left hand movement task. Moreover, HAART could influence BOLD signals in HIV+ patients and different combinations of HAART drugs exerted varying effects.

fMRI plays an important role in noninvasive visualization of the function and connection of motor cortex [16]. However the cerebral changes of HIV-infected patients without HAND in the early stage were seldom reported. Therefore this study provides evidence that although HIV patients had no deficit of finger movement, and BOLD signals related to hand movement task could detect early deficits in the motor-related brain area of HIV+ group. As indicated in this study, HIV+ patients were found with increased BOLD signals during right-hand movement. HIV patients with HAND have deficits in attention and working memory. fMRI data indicated that the ventral prefrontal cortex was less active in HIV+ subjects than the control in semantic event sequencing while postcentral and supramarginal gyrus was hyperactive in HIV+ subjects. Clinical examination showed that index finger movement and extension were slow in the HIV-infected patients [17]. The results suggested that ahead of the presence of HIV-associated neurological disorders, the function and cooperation of the brain underwent changes which may cause some deficits in central nervous system of HIV infected patients.

Brain asymmetrical deficits were also observed in HIV+ subjects of this study. During the right hand movement task, HIV+ subjects showed greater activity than the control; while during the left hand movement, these two groups indicated no significant difference. This suggested that the motor function was more unilateral in HIV+ patients and the increased laterality was due to the weakened motor−related activity in the right hemisphere. Thus we proposed that although HIV+ patients did not manifest cognitive deficits, there still exist HIV-incurred brain damages as indicated by the lateralization of motor functions. Ipsilateral postcentral gyrus and contralateral cerebellum were correlated with normal motor function, and the activation of anterior cingulum and precuneus proved the presence of some structurally associated deficits. Brain asymmetry is reflected in anatomical and functional difference in left and right hemisphere, which is usually defined as lateralization [18,19]. Meanwhile, the lateralization can be discovered during emotional process and language process [20]. Numerous studies reported that patients with schizophrenia exhibited decreased hemispheric lateralization including motor and language functions as disclosed by fMRI motor and speech tasks [21−23]. Several fMRI studies pointed out that the right-handed people had preference of the left hemisphere in motor function experiments [22,24].

Previous studies with BOLD to measure the physiological and neurocognitive deficits in HIV+ patients always covered both patients with and without HAART. It has been recognized that since the introduction of HAART therapy, the life of HIV-infected patients has been improved. HAART is customized containing medications that could prevent the onset of AIDS symptoms. Common regimens encompass two nucleoside reverse inhibitors (NRTIs) and a protease inhibitor (PI), or two NRTIs and a non-nucleoside reverse inhibitors (NNRTI) or other combined drugs. HAART is primarily aimed to suppress DNA synthesis and duplication as well as HIV replication in the plasma and central nervous system. The cognition test by Sacktor consolidated that HAART could achieve greater improvement of psychomotor slowing [25,26]. However, there is no report whether HAART could change BOLD signals in HIV+ patients. This study investigated the relationship between antiretroviral medications and fMRI signals by comparing the signal changes of HIV+ patients with and without HAART. HAART was found able to significantly attenuate the higher BOLD signals, the result of more usages of brain in HIV+ patients. Thus we hypothesizes that HAART medication is necessary in improving the neurocognitive functions prior to the occurrences of deficits in HIV+ subjects. Furthermore, compared with the ATE group, the other group was detected with higher signals in the caudate and middle cingulum gyrus, validating thatATE could suppress the functions of such areas, which has not been reported. Additionally, different medication regimens had varying effects on brain functions. Since the cingulum, as a frontal association tract, is intimately correlated with cognitive functions, the suppression of cingulum could exert positive effects on cerebral signal changes of HIV+ patients.

Considering that there were a few homosexual subjects in HIV+ group, the possibility that sex orientation might affect brain asymmetry can not be excluded [27,28]. Therefore, the relationship between sex orientation and functional asymmetry will be explored in further studies.

Acknowledgment

The study was supported by Beijing Natural Science Foundation, No. 7132108.

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